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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
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08/447,820 05/23/95 EKINS

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HM21/0330

DANN DORFMAN HERRELL AND SKILLMAN
SUITE 720
1601 MARKET STREET
PHILADELPHIA PA 19103-2307

EXAMINER

WOODWARD, M

ART UNIT	PAPER NUMBER
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1643

14

DATE MAILED:

03/30/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

NOTICE OF ALLOWABILITY

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be mailed in due course.

☒ This communication is responsive to AMEND D (PAPER No. 12) & DECL. (PAPER No. 13)

☒ The allowed claim(s) is are 1-17

☐ The drawings filed on _____ are acceptable.

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serail Number) _____

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE THREE MONTHS FROM THE "DATE MAILED" of this Office action. Failure to timely comply will result in ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.

☒ Applicant MUST submit NEW FORMAL DRAWINGS

☐ because the originally filed drawings were declared by applicant to be informal.

☒ including changes required by the Notice of Draftperson's Patent Drawing Review, PTO-948, attached hereto or to Paper No. 4

☐ including changes required by the proposed drawing correction filed on _____, which has been approved by the examiner.

☐ including changes required by the attached Examiner's Amendment/Comment.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the reverse side of the drawings. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftperson.

☐ Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any response to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE/SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Notice of Draftperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☐ Interview Summary, PTO-413

☒ Examiner's Amendment/Comment

☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material

☒ Examiner's Statement of Reasons for Allowance



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

NOTICE OF ALLOWANCE AND ISSUE FEE DUE

HM21/0350

DANN DOREMAN HERRELL AND SKILLMAN
SUITE 720
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PHILADELPHIA PA 19103-2307

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
08/447,820	05/23/95	017	WOODWARD, M 1643	03/30/98
First Named Applicant	EKINS, ROGER P.			

TITLE OF INVENTION DETERMINATION OF AMBIENT CONCENTRATIONS OF SEVERAL ANALYTES

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1	436-518.000	025	UTILITY	NO	\$1320.00	06/30/98

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

HOW TO RESPOND TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

- A. If the status is changed, pay twice the amount of the FEE DUE shown above and notify the Patent and Trademark Office of the change in status, or
- B. If the status is the same, pay the FEE DUE shown above.

If the SMALL ENTITY is shown as NO:

- A. Pay FEE DUE shown above, or
- B. File verified statement of Small Entity Status before, or with, payment of 1/2 the FEE DUE shown above.

II. Part B-Issue Fee Transmittal should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B Issue Fee Transmittal should be completed and returned. If you are charging the ISSUE FEE to your deposit account, section "4b" of Part B-Issue Fee Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give application number and batch number.

Please direct all communications prior to issuance to Box ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

Serial No. 08/447,820
Art Unit 1643

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

The first paragraph of the specification has been amended to include:

E1, filed as PCT/GB88/00649, Aug 5, 1988.

37

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to **Group Art Unit 1643**.

5 The following is an examiner's statement of reasons for allowance:

 The rejection of claims 1-3 under 35 U.S.C. § 102(a) as being clearly anticipated by Ekins et al. (1989) is withdrawn in view of applicant's claim to priority to GB 8803000.

10 The rejection of claims 1 and 2 under 35 U.S.C. § 102(b) as being clearly anticipated by Ekins (WO 88/01058) is withdrawn in view of applicant's claim to priority to GB 8803000.

15 The rejection of claim 3 under 35 U.S.C. § 103 as being unpatentable over Ekins (WO 88/01058) in view of the commercial availability of the Bio-Rad Laserssharp MRC 500 is withdrawn in view of applicant's claim to priority to GB 8803000.

Declarations of Berger, Ekins and Woodhead

 The Declarations of Berger, Ekins and Woodhead under 37 CFR 1.132 filed November 28, 1997 and March 5, 1998 have been considered.

 To put it most simply each declaration fails to consider the Ekins teachings,

rather each declarant predicates his arguments on the departure from conventional wisdom that Ekins represents. But this is not the issue. The issue is given the Ekins teachings what would one of ordinary skill in the art have found obvious at the time the instant invention was made. It may well be that at the time Ekins proposed his fractional occupancy method that it was greeted with disbelief, however, such disbelief does not render its teachings invalid. It would appear to be each of declarants thesis that this disbelief would prevent a person of ordinary skill in the art from analyzing and verifying the teachings of Ekins. That such teachings were apparently at odds with conventional wisdom speaks to their novelty at the time of Ekins. It is equally illogical to predict results of the Ekins method based on conventional methodology given its radical departure. Thus, while the teachings in the art concerning the amount of binding agent necessary for classical immunometric assays are of interest to one attempting to employ the teachings of Ekins but they are not pre-conditions thereof. Given the fundamental departure which Ekins represents one is forced to evaluate it on its own terms and not those which existed prior thereto.

In particular at paragraph 5 of his declaration Ekins states:

There is no reason to suppose that Ekins '031 would overturn these views since it relates solely to the design of assays which are sample-volume independent and does not address the issue of sensitivity.

These statement is astonishing given that Ekins '031 represents a paradigm shift with respect to immunoassays.

Both Ekins and Woodhead allege that Ekins ('031) does not address the issue of highly sensitive immunoassays. The basis for such allegations is unclear since Ekins ('031) sets forth the following:

An added advantage of the use of fluorescent labels or others of very high specific activity for analyte-labelling is that they make possible the development of very high sensitivity, multiple-analyte, assays relying on the scanning of the distribution of fluorescent labels (comprising labelled antibodies and/or labelled analytes) deposited on the surface of - for example- a suitable plastics material. Such a surface-"printed" with a mixture of different antibodies and subsequently exposed to the biological fluid under test- can potentially be used to reveal the concentration of many different analytes in the same sample- a requirement which is likely to become increasingly pressing in the monitoring of blood for the presence of complex mixtures of viral antigens and/or antibodies [sic], tumour antigens, hormones, etc.

It appears to the examiner that Ekins is speaking to sensitive immunoassays employing the teachings of his application. Should applicant or his declarants traverse the examiner's position in this regard such traversal should be accompanied by objective evidence.

It is noted that both Ekins and Woodhead allege that unexpected results are afforded by the now claimed invention, in particular that enhanced sensitivity is obtained. Regrettably neither declarant offers more than his opinion.

It is completely unclear to the examiner how Woodhead can conclude that "it seemed to me that while the concept was attractive, the requirement to reduce the

amount of binding reagent in such assays would inherently restrict their application to situations where high sensitivity was not required,” in the face of the teachings from pages 5 and 6 quoted above the examples of the Ekins ('031) application. On what objective fact pattern does Woodhead base his inherency.

5 At paragraph 7 Ekins quotes the examiner as stating “in order to employ the Ekins assay one must know the amount of binding agent present.” Ekins then states:

 In the sense implied by the Examiner this is wholly untrue.

10 Ekins is invited to explain how it is that the method of Ekins ('031) can be practiced without a knowledge of the amount of binding agent immobilized. Ekins should explain how it is that Ekins ('031) explicitly teaches making such a measurement if such a measurement is not required. Additionally, Ekins should explain how it is that a measurement of “fractional occupancy” can be made absent a knowledge of the total number of sites available.

15 Further, Ekins should explain how it is that his assay is insensitive to variations in the amount of antibody immobilized. Such an explanation is necessary as it is key to refuting the examiner’s argument that an accurate determination of “fractional occupancy” requires knowledge of the total number of available sites as well as the number of sites occupied.

20 Ekins’ argument in paragraph 8 speaks to an unclaimed embodiment. Basically Ekins is asserting that one need not know how much binding agent is immobilized over the entirety of a spot and need not scan an entire spot since all that is of concern is the fractional occupancy of the immobilized sites. However, the measurement of even a portion of a site is fundamentally the same as measuring the
25 entire site since one is measuring total sites and filled sites over a particular area.

The key to the instantly claimed invention and that of Ekins ('031) is measurement of sites and their occupancy.

There is a difference and that difference resides in how the measurement of total sites is made. In Ekins ('031) such a determination is made from a Scatchard plot whereas in the instant case total sites are estimated from a signal originating
5 from the immobilized reagent.

In paragraph 8 Ekins asserts that the teachings of the instant application are "quite contrary" to those of Chen. This is simply not the case. Chen recognized the problem of variations in the substrate employed for immobilization of binding
10 reagents and sought to control for it by determining how much reagent was immobilized in a particular area. Chen sought uniformity so as to minimize variations in signal arising from variation in the amount of immobilized reagent. Ekins is correct that this is a type of quality control. Nonetheless Chen is teaching a means for determining the total sites present in a particular area. Since such
15 knowledge of total sites is necessary to accurately apply the Ekins binding equation one would have utilized the method of Chen for determining the total sites immobilized rather than the Scatchard analysis employed by Ekins ('031).

It is unclear to the examiner how a measurement of sites in a localized area of a larger spot is different from measurement of sites in a spot the size of the localized
20 area. It is noted that this is not a limitation of the claims.

Applicant's arguments spanning pages 6 and 7 are at best disingenuous. Applicant's method is not independent of the amount of receptor used since the maximum amount which can be employed is defined by the necessity of keeping it below the level at which it significantly interferes with free analyte concentration. It
25 is either factually inaccurate to assert that variation in the amount of immobilized

material does not matter or else one is assuming that the variation in amount immobilized is insignificant. In order to practice the claimed invention most accurately a determination of the total number of sites present must be made. If variation in the amount were irrelevant it would not be necessary to experimentally measure the sites since one could simply assume that the number of sites present was constant across the entire surface. But as has been acknowledged the lack of uniformity in immobilization substrates is well known in the art.

Gordon et al. (US 5,486,452)

The examiner herein makes Gordon et al. (US 5,486,452) of record. Gordon et al. evolved from UK 2,099,578 which applicant extensively discusses in his specification. Particular attention is drawn to its teachings with regard to immobilizing reagents in small spots, e.g. less than 1 mm². Gordon et al. also discloses employing a plurality of spots for the same or different analytes and suggests detection of bound analyte through a plurality of means including fluorescent markers.

Obviousness of 0.1 V/K

Ekins ('031) teaches that it is a requirement that the change in level of free analyte be insignificant in order to practice his assay. The lowest value explicitly taught in Ekins ('031) has been calculated by applicant to be 0.25 V/K whereas the current claims recite that a value of less than or equal to 0.1 V/K be employed. Applicant has further calculated that Ekins discloses assays with V/K and 0.5 V/K. Ekins ('031) discloses a range of values over which his assay is functional.

Ekins disclosure is of a range of values of V/K over which his method is functional. There is no clear suggestion in Ekins to go below a value of 0.25 V/K or that it would be advantageous to do so.

It is this absence of suggestion which renders the instant claims unobvious and therefore allowable.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably
5 accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MP Woodward whose telephone number is (703) 308-3890. The examiner can normally be reached on Monday-Friday from 7:30
10 AM to 5:00 PM. In the event that the examiner does not personally answer the telephone his voice mail will provide the necessary instructions.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marian Knode, can be reached on (703) 308-4311.

Currently a plurality of official and unofficial fax lines are available.
15 However, changes in fax location occur with frequency. Please contact the examiner to obtain the currently operative fax numbers.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MPW
MICHAEL P. WOODWARD
PRIMARY EXAMINER
AU 1643
March 26, 1998